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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/732,546 | 12/08/2000 | Celia Dominguez | A-648 | 4170 |

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| EXAMINER |
|---|
| RAO, DEEPAK R |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

DATE MAILED: 05/14/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/732,546 | Dominguez et al. |
| **Examiner** | **Art Unit** |
| Deepak Rao | 1624 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Feb 22, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1, 2, and 4-18* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, and 4-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1-2 and 4-18 are pending in this application.

### *Election/Restriction*

Applicant's election with traverse of Group I, claims 1-2 and 4-18, drawn to compounds wherein A is pyrrolidiyl and V is a carbocyclic radical in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the restriction is improper because there is no burdensome search involved in searching Groups I and II together. This is not found persuasive because as explained in the previous office action, the compounds of groups I-II are drawn to structurally dissimilar compounds which are not art recognized equivalents. They are structurally dissimilar such that a reference anticipating a compound may not render the remaining compounds obvious. 37 CFR 1.141(a) provides that two or more independent and distinct inventions may not be claimed in one application, whether or not the misjoinder occurred in one claim or more than one claim. Restriction is going to be exercised where independent and distinct inventions are presented in one Markush grouping. Independent means when the compound is being made and/or used alone, not in combination with other compounds of the Markush expression. Restriction is considered proper in Markush claims where the members are so diverse and unrelated that a prior art reference anticipating the claim with respect to one of the members, would not render the claims obvious under 35 U.S.C. 103 with respect to the other members. Therefore, what should be considered for patentable distinctness is the compound as a whole.

Each of the groups are classified diversely based on the various definitions of A, V, etc. and further, the compounds of Groups I-II require separate searches in the literature and therefore, it is **burdensome** for the examiner.

The requirement is still deemed proper and is therefore made FINAL.

### *Claim Rejections - 35 U.S.C. § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of diseases such as rheumatoid arthritis, does not reasonably provide enablement for the treatment of all other diverse disorders embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The specification fails to enable one skilled in the art to use the instantly claimed compounds. The use disclosed in the specification is as integrin receptor modulators useful to treat a variety of diseases, see specification pages 27-28. Biological assays to test the activity of the compounds are provided on pages 153-159, and it is concluded that certain compounds of the invention exhibited $IC_{50}$ values of 30μM or less, see page 159. There is no reasonable basis for assuming that the myriad of compounds embraced by the instant claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art (directed to integrin receptor modulators) for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also, see MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally an unpredictable and highly structure specific area.

Further, claims are drawn to a method of treating a myriad of diseases with different etiologies such as angiogenesis, inflammation, cancer, metastasis, bone resorption related diseases, viral infections, etc. It is inconceivable as to how the claimed single class of compounds can treat the vast list of diseases recited in the claims having diverse mechanisms. See the unpredictability of the ligand-receptor interactions reported in state of the art. Kim et al. (cited in IDS), in their publication indicated that "The complex functions of the vitronectin molecule are poorly understood" (see page 26929). Schvartz et al. (cited in IDS) remarked that "it is rather difficult to establish unequivocally the overall regulatory role of vitronectin, its

involvement in pathogenesis and its importance as a target for pharmacological intervention" (see page 544). Raynal et al. (cited in IDS) stated that "Further studies are required to explain the different mechanisms of action of BSP in osteoclast differentiation and bone resorption" (see page 2352). Therefore, the state of the art provides that the activity of various integrin receptors or the modulators thereof is very unpredictable, which emphasizes the requirement of undue experimentation in determining the corresponding therapeutic activity.

For example, angiogenesis is the process of vascularization of a tissue involving the development of new capillary blood vessels and therefore, is not seen as being a disease or disorder, but as an absolutely essential body process. Thus, there is no enablement for treating something which is not itself a problem and is indeed essential for life.

Similarly, enablement for the scope of 'inflammation' generally is not present. For a compound or a genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any site or any part of the body. There is no common mechanism by which all, or even most inflammations arise. Mediators include bradykinin, serotonin, histamine, leukotriene, cytokine, and many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation, and there is no "magic bullet" against inflammation generally.

Further, the claims specifically recite 'treatment of viral infections', however, there is no common mechanism by which all conditions due to viral infections arise. There are more than 400 distinct viruses that infect humans producing a wide range of diseases. Cecil Textbook of

Medicine states that "for many viral infections, no specific therapy exists. Proper use of antivirals requires specific viral diagnosis" (see the enclosed article, page 1742). Roivainen et al. (cited in IDS) in their article discussing virus-integrin interactions, concluded that the study requires 'further investigation' (see page 364). Also, Agrez et al. (Virology, cited in IDS) in their publication stated that "The mechanisms by which integrins mediate endocytosis of viruses are not known" (see page 75).

The claims also recite 'cancer', 'metastasis'. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Further, see the publication by Agrez et al. (Int. J. Cancer, 1999, cited in IDS), wherein it was stated that "In human cancers, the co-operative role between cell adhesion and proteases of degrading matrix barriers remains poorly understood" (see page 90). Gladson et al. (cited in IDS) regarding vitronectin related *in vitro* / *in vivo* activity, expressed that "the physiological significance of this is unclear as vitronectin is not detectable in

most undifferentiated neuroblastomas *in vivo*" (see page 1641). Nip et al. (cited in IDS), in their article concluded that there are many "unanswered questions" in the role of integrin receptors with respect to melanoma metastasis (see pages 247-249). Also, Brooks et al. (cited in IDS) provide that "the mechanisms by which these [integrin] antagonists inhibit tumor metastasis are not completely understood" (see page 457). Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds for the treatment of the diverse disorders instantly claimed.

### *Claim Rejections - 35 U.S.C. § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior

> art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 4-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abood et al., U.S. Patent No. 5,721,366. The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula (I) in col. 2 wherein X is -C(O)-NH- (as defined in col. 3) and further see the specific compounds of Examples 11, 15 and 17. The compounds are taught to be useful as pharmaceutical therapeutic agents, see col. 3, lines 21-26. The claims differ from the reference by reciting a specific species and/or a more limited genus than the reference. The instant compounds differ from the reference compounds having the side chain on the pyrrolidinone at position different from the reference compounds. See for example, reference compound of Example 11 wherein the side chain containing the amido group is attached to the carbon atom adjacent to the ring member carrying the oxo substituent, as compared to the instant claims wherein the point of attachment is through the carbon atom which

is separated from the carbonyl ring member by another carbon atom. In other words, the reference teaches 3-substituted compounds and the instant claims are drawn to 4-substituted compounds (ring members numbered starting from nitrogen as 1, carbonyl as 2, etc.). It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, i.e., as therapeutic agents. It has been held that a compound which is isomeric with a compound of prior art is prima facie obvious absent unexpected results. *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950); *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

Note that claims 9-18 are drawn to treatment of diseases modulated by an integrin receptor and the specification identifies these diseases to be inflammation, metastasis, etc. (see page 7). The reference also teaches that the reference compounds are useful as therapeutic agents having platelet aggregation inhibitory activity (see col. 3) and further, such diseases are indicated to include inflammation, metastasis, etc., see col. 2, lines 5-7.

***Oath/Declaration***

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The citizenship of Nianhe Han has been changed without initials/date.

***Information Disclosure Statement***

Receipt is acknowledged of the Information Disclosure Statement filed on October 29, 2001 and a copy is enclosed herewith. The submitted references DP, DQ, DV, EA, ES, FD and FN did not indicate the pertinent pages relevant to the instant invention and did not include such pages. The references only contained Table of Contents in the cited books. Therefore, these references were not considered, see 37 CFR 1.98(b) which requires the publication to include relevant pages.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm. The fax phone number for

the organization where this application or proceeding is assigned is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
May 10, 2002